Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2019;44(4):1333-1338
DOI: 10.17826/cumj.531969

ARAŞTIRMA / RESEARCH

Neutrophil-to-lymphocyte ratio independently predicts the epicardial fat thickness in diabetic patients

Nötrofil/lenfosit oranı diyabetik hastalarda epikardiyal yağ doku kalınlığının bağımsız bir belirleyicisidir

Yasar Turan[1], Elif Turan[2]

[1] Bozok University, Faculty of Medicine Department of Cardiology, [2]Department of Endocrinology and Metabolic Disease, Yozgat, Turkey

Cukurova Medical Journal 2019;44(4):1333-1338.

Abstract

Purpose: The aim of this study was to investigate neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and epicardial fat thickness (EFT) in diabetic and non-diabetic patients, and to determine the factors affecting EFT in diabetic patients.

Materials and Methods: In this cross-sectional study, 92 diabetic patients and 40 healthy volunteers without diabetes, admitted to our outpatient clinic, were included. Demographic data, anthropometric measurements, biochemical and hematological results, echocardiography findings and EFT were recorded. NLR and PLR were calculated. These values were compared statistically between the two groups.

Results: The two groups were similar in terms of age, gender, smoking status, diastolic blood pressure, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein and PLR. Body mass index (BMI), frequency of hypertension, systolic blood pressure, serum glucose, HbA1C, serum creatinine, triglyceride, total cholesterol/HDL, NLR and EFT were significantly higher in the diabetic group than the control group. Ejection fraction was significantly lower in diabetic group than the controls. NLR and BMI were independent predictors of EFT in diabetic patients.

Conclusion: We suggest that echocardiographic EFT measurement, NLR and BMI might be useful in the evaluation of cardiovascular risk in diabetic patients.

Keywords: Diabetes mellitus; epicardial fat thickness; inflammation; neutrophil-to-lymphocyte ratio.

Öz

Amaç: Çalışmamızda diyabetik ve diyabetik olmayan hastalarda nötrofil/lenfosit oranı (NLR), platelet/lenfosit oranı (PLR) ve Eeikardiyal yağ dokusu kalınlığını (EFT) karşılaştırmayı ve diyabetik hastalarda EFT'yi etkileyen faktörleri belirlemeyi amaçladık.

Gereç ve Yöntem: Bu kesitsel çalışmada polikliniğimize başvuran ve diyabeti olan 92 hasta ile birlikte, diyabeti olmayan 40 sağlıklı gönüllü çalışmaya dahil edildi. Tüm katılımcıların özgeçmişi, boy, kilo, vücut kütle indeksleri (BMI), sigara alışkanlıkları, fizik muayene bulguları, biyokimyasal ve hematolojik sonuçları ve ekokardiografi bulguları kaydedildi. Bu değerler iki grup arasında istatistiksel olarak karşılaştırıldı.

Bulgular: Gruplar yaş, cinsiyet, sigara alışkanlığı, diyastolik kan basıncı, total kolesterol, high-density lipoprotein (HDL), low-density lipoprotein ve PLR açısından benzerdi. BMI, hipertansiyon, sistolik kan basıncı, serum glukoz, HbA1C, serum kreatinin, trigliserid, total kolesterol/HDL oranı, NLR ve EFT diyabetik hastalarda kontrol grubuna göre istatistiksel olarak anlamlı şekilde yüksek, ejeksiyon fraksiyonu ise anlamlı olarak düşüktü. NLR ve BMI diyabetik hastalarda EFT'nin bağımsız prediktörü olarak tespit edildi.

Sonuç: Ekokardiografik EFT ölçümü, basit hematolojik parametrelerden biri olan NLR ve son olarak BMI diyabetik hastalarda kardiovasküler risk değerlendirilmesinde kullanılabilir.

Anahtar kelimeler: Diyabetes mellitus; epkardial yağ dokusu; inflamasyon; nötrofil/lenfosit oranı

Yazışma Adresi/Address for Correspondence: Dr. Elif Turan, Medical School of Bozok University, Department of Endocrinology and Metabolic Disease, Yozgat, Turkey E-mail: drelifturan@hotmail.com
Geliş tarihi/Received: 25.02.2019 Kabul tarihi/Accepted: 09.04.2019 Çevrimiçi yayın/Published online: 15.09.2019

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is the most common metabolic disorder in adults. T2DM is strongly associated with inflammation. Chronic inflammation contributes to the development and progression of chronic complications resulting from micro and macroangiopathic changes in diabetic patients[1,2]. Microvascular complications are diabetic retinopathy, nephropathy and neuropathy, while, the most important macrovascular complications are cardiovascular diseases (CVD). CVD is the major cause of morbidity and mortality in patients with diabetes mellitus (DM)[3].

Epicardial adipose tissue is a small but biologically active ectopic fat depot between the visceral layer of the myocardium and the pericardium. Increased epicardial fat thickness (EFT) has been shown to be associated with coronary artery disease (CAD)[4]. In patients with CAD, increased epicardial fat becomes inflammatory and may promote plaque development through secretion of proinflammatory cytokines and by the other mechanisms. Therefore, EFT may be a biomarker of cardiovascular risk and a potential therapeutic target for CVD[5].

The count of white blood cell and subtypes may basically reflect infection and/or inflammatory processes. In recent years, the presence of neutrophilia and relative lymphopenia has been investigated as a marker in several clinical conditions and diseases. Neutrophil-to-lymphocyte ratio (NLR) has been proven to be superior to leukocytes as a marker of inflammation[6]. Recently, NLR and platelet-to-lymphocyte ratio (PLR) are studied as the new parameters determining the inflammation in CVD[7].

We aimed to investigate NLR, PLR and EFT in diabetic and non-diabetic patients, and to determine the factors affecting EFT in diabetic patients.

MATERIALS AND METHODS

This cross-sectional study included 92 consecutive T2DM patients who attended our endocrinology outpatient clinic, and 40 healthy controls without DM, between January 2016 and September 2017. Written informed consent was obtained from all patients before enrollment. Patients with known CVD, heart failure, severe valvular disease, chronic obstructive pulmonary disease, infection, chronic inflammatory disease, chronic liver or renal diseases, peripheral arterial disease and pregnant or nursing women were excluded. All patients were questioned for the risk factors of CVD. Demographic data and anthropometric measurements were recorded. Body mass index (BMI) was calculated as weight (kg)/height (m^2). Blood pressures were measured by standard sphygmomanometer after 5-minute rest. Hematological parameters, serum glucose, lipid profile and HbA1C parameters were studied over a 12-hour fasting period. The study protocol was approved by the ethics committee of Bozok University and the study was conducted according to the principles of the Declaration of Helsinki.

Measurement of epicardial fat thickness

All patients were referred to the cardiology outpatient clinic for cardiac evaluation. After a detailed physical examination, transthoracic echocardiography imaging was performed in all participants in the left lateral position according to the American Society of Echocardiography guidelines using a Philips Logic Affiniti 50G machine (Philips, Amsterdam, Netherlands) and a broadband transducer with simultaneous electrocardiogram follow-up[8].

Echocardiography was done by the same cardiologist who was unaware of the clinical data. EFT was identified as the relatively echo free space between the outer wall of the myocardium and the visceral layer of pericardium. EFT was measured from the long axis and apical four chamber view, perpendicularly on the free wall of the right ventricle at end-diastole in three cardiac cycles.

Statistical analysis

All analyses were conducted using SPSS version 18.0 (SPSS for Windows, Chicago, IL). Baseline characteristics were expressed in numbers and percentage. Continuous variables were expressed as mean ± standard deviation. Comparisons of categorical variables between groups were performed using the chi-square test. Comparisons of continuous variables among the groups were performed using independent samples T test for variables distributed normally and Mann-Whitney U test for variables distributed non-normally. Possible correlations between demographics, laboratory results, hemodynamic and echocardiographic parameters were assessed by Pearson or Spearman's correlation analysis, as appropriate.

A linear regression analysis was performed for finding independent predictors of EFT in diabetic patients. Variables that had a p< 0.2 in the univariate analysis were included in the multivariable models. For all statistical tests, P<0.05 was considered significant.

RESULTS

The baseline characteristics of 92 T2DM patients and 40 control subjects were shown in Table 1. The groups were similar in terms of age, gender, smoking status, diastolic blood pressure, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and PLR (P>0.05 for all). The frequency of hypertension was significantly higher in the T2DM group than the controls (45% vs. 20%; p=0.009). BMI (33.94±6.35 vs. 30.25±6.10; p=0.003), systolic blood pressure (135.9±20.1 vs. 124.3±15.1; p= 0.001), serum glucose (210.7±97 vs. 96.1±7.9; p<0.001), HbA1C (9.16±2.16 vs. 5.62±0.39; p<0.001), serum creatinine (0.84±0.21 vs. 0.74±0.1; p=0.006), triglycerides [172 (86-971) vs. 116 (55-510); p=0.009], total cholesterol/HDL (4.55±1.5 vs. 4.06±0.9; p=0.035), NLR (2.32±1.1 vs. 1.72±0.61; p=0.002) and EFT (5.82±1.22 vs. 4.38±1.21; p<0.001) were significantly higher in the T2DM group than the control group. Left ventricular ejection fraction was significantly lower in the T2DM group than the control group (60.88±3.47 vs. 62.37±3.06; p=0.021).

Correlation analysis showed that EFT was positively correlated with age (r:0.243, p:0.019), BMI (r:0.262, p:0.012), diabetes duration (r:0.232, p:0.026), HbA1C (r:0.235, p:0.024), NLR (r:0.260, p:0.012), and PLR (r:0.212, p:0.043) in patients with T2DM (Table 2). Multivariate linear regression analysis revealed that NLR (0.362, CI: 0.154-0.571, p=0.001) and BMI (0.048, CI: 0.011-0.085, p=0.011) were independently associated with EFT in patients with T2DM.

Table 1. Demographic and clinical data of the participants.

Characteristics	Control group (n = 40)	Diabetes Mellitus (n=92)	p
Age, years	48.28±6.99	49.53±4.1	0.180
Gender, n (male/female)	13/27	35/57	0.543
Body mass index, kg/m^2	30.25±6.10	33.94±6.35	0.003
Hypertension, n (%)	8/32	42/50	0.009
Smoking, n (%)	9/31	22/70	0.860
Diabetes duration, years	-	10.62±5.5	-
Systolic Blood Pressure (mmHg)	124.3±15.1	135.9±20.1	0.001
Diastolic Blood Pressure (mmHg)	78.7±9.8	82.2±10.2	0.071
Serum glucose (mg/dL)	96.1±7.9	210.7±97	<0.001
HbA1C (%)	5.62±0.39	9.16±2.16	<0.001
Serum creatinine (mg/dL)	0.74±0.1	0.84±0.21	0.006
Total cholesterol (mg/dL)	193.9±45.9	200.9±56.2	0.213
Triglyceride (mg/dL)	116(55-510)	172 (86-971)	0.009
HDL (mg/dL)	48.56±9.3	46.84±16.3	0.055
LDL (mg/dL)	121.0±36.2	120.7±36.6	0.954
Total/HDL	4.06±0.9	4.55±1.5	0.035
NLR	1.72±0.61	2.32±1.1	0.002
PLR	113.28±20.2	129.03±51.4	0.064
Ejection fraction (%)	62.37±3.06	60.88±3.47	0.021
Epicardial fat thickness (mm)	4.38±1.21	5.82±1.22	<0.001

Continuous variables are presented as mean ± SD, and the categorical variables as n (%).
HDL: High-density lipoprotein, LDL: Low-density lipoprotein, Total/HDL: Total cholesterol-to-HDL ratio, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio.

DISCUSSION

The main findings of our study were; NLR, as a simple marker of inflammation, total cholesterol/HDL, as a cardiovascular risk marker, and EFT, as noninvasive marker of inflammation and subclinic atherosclerosis, were higher in diabetic patients compared to the control group. Furthermore, NLR and BMI were the independent predictors of EFT in diabetic patients.

Table 2. The correlation between epicardial fat thickness and clinical/demographic variables in diabetic patients.

Variables	EFT	
	r	p
Age	0.243	0.019
Body mass index	0.262	0.012
Diabetes duration	0.232	0.026
Systolic Blood Pressure	0.190	0.070
Diastolic Blood Pressure	0.068	0.520
Serum glucose	0.067	0.524
HbA1C	0.235	0.024
Serum creatinine	0.042	0.693
Total cholesterol	0.087	0.410
Triglyceride	0.173	0.098
HDL-C	-0.034	0.747
LDL-C	0.017	0.870
Total/HDL	0.116	0.271
Ejection fraction	0.164	0.119
NLR	0.260	0.012
PLR	0.212	0.043

HDL: High-density lipoprotein, LDL: Low-density lipoprotein, Total/HDL: Total cholesterol-to-HDL ratio, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio.

Cardiovascular diseases are the most common cause of mortality in diabetic patients (70%)[9]. Due to the increased cardiac mortality and morbidity risk, DM is suggested as CAD equivalent. DM accelerates atherosclerosis. This is a cumulative result of the high incidence of cardiovascular risk factors such as hypertension, hyperlipidemia and other metabolic disorders in patients with DM. Notwithstanding, hyperglycemia induces inflammation causing a chronic inflammatory state in DM[9].

Inflammation plays a role in the pathogenesis of CVD and, therefore, inflammatory biomarkers are recently frequently investigated. NLR is an inflammatory marker reported to be associated with the severity and prognosis of many CVD types[10]. In a large cohort of patients with DM and metabolic syndrome, NLR was associated with both metabolic syndrome and risk of ischemic CVD[11]. Azab et al. reported that, major adverse cardiac events that include acute myocardial infarction, coronary revascularization, and mortality in 4-year follow-up, was associated with NLR, moreover, NLR was an independent predictor of major adverse cardiac events in diabetic patients[12]. In accordance with the previous data, NLR was found to be higher in patients with T2DM in our study.

In our study, the triglyceride levels of the diabetic patients were higher than the control group, but no significant difference was found in LDL, HDL and total cholesterol levels. Atherogenic dyslipidemia with low HDL and high triglyceride is a common lipid profile in diabetic patients and it is associated with silent myocardial ischaemia in patients with T2DM[13]. Increased triglyceride level is shown to be associated with higher CVD mortality in the Diabetes Heart Study[14]. In our study, total cholesterol/HDL ratio was significantly higher in diabetic patients. A 10-year cohort study conducted in Turkey (TEKHARF), reported that total cholesterol/HDL ratio was the only significant independent lipid variable in predicting future coronary death and cardiovascular events[15].

The epicardial fat accounts only 1% of whole fat mass. However, these epicardial adipocytes are able to produce several bioactive molecules. These bioactive molecules, including inflammatory cytokines, secreted from EFT might directly affect the coronary arteries and the myocardium and may have a role on cardiac function. In this manner, increased EFT is reported to be associated with the progression of cardiac dysfunction in obese individuals[16].

In our study, EFT measurements and BMI were significantly higher in diabetic patients compared to the control group. Considering the chronic inflammatory state in DM, the epicardial fat and secreted bioactive cytokines can be cofactors contributing to this process. In the regression analysis, NLR and BMI were identified as the independent predictors of EFT in diabetic patients. Previous studies have reported higher anthropometric measurements in T2DM[17]. Obesity is a common health care problem that increases gradually. It is associated with the development and progression of both DM and its subsequent cardiovascular pathologies. Data are available showing that obesity is associated with CVD, and CAD[18]. Furthermore, abdominal visceral adiposity is closely correlated with the risk of CVD[19]. Epicardial fat substantially increases with obesity and EFT is a good predictor of abdominal visceral adiposity[20,21].

In our study, another independent predictor of EFT was the NLR in diabetic patients. There are studies aiming to determine the relationship between inflammatory markers and EFT. Akbas et al. have

reported that NLR and PLR were correlated with EFT but only the waist circumference was independently associated with EFT in diabetic patients[22]. In our study, there was no difference between the groups in terms of the PLR, but there was a positive correlation between EFT and PLR in diabetic patients. Ozçiçek et al. have reported that NLR was an independent predictor of EFT in hemodialysis patients[23]. The significant relationship between NLR and EFT that identified in our study may be attributed to the chronic low-grade inflammation in DM. NLR and EFT may be common indicators of the complex inflammatory process in diabetes.

Our study has several limitations. Firstly, this was a cross-sectional study with a relatively small sample size and interpretation of the observed associations might be restricted with regard to cause and effect. Secondly, we used a two dimensional echocardiographic measurement and it may be not enough to show the total amount of epicardial fat. Thirdly, it reflects a single center experience, therefore, the external validity of the results for different populations and settings is potentially limited. Fourthly, the correlations between the variables were relatively weak in our study. Our findings need to be confirmed in other prospective studies with larger populations and long-term clinical follow-up.

In conclusion, EFT was significantly higher in diabetic patients. Furthermore, NLR and BMI were independent predictors of higher EFT in diabetic patients. There is a complex relation between diabetes, obesity, inflammation and CVD. NLR as a simple marker of inflammation and BMI as a marker of obesity may be useful in determining the cardiovascular risk in diabetic patients.

Yazar Katkıları: Çalışma konsepti/Tasarımı: YT, ET; Veri toplama: ET, YT; Veri analizi ve yorumlama: ET, YT; Yazı taslağı: YT, ET; İçeriğin eleştirel incelenmesi: YT; Son onay ve sorumluluk: YT, ET; Teknik ve malzeme desteği: ET, YT; Süpervizyon: YT; Fon sağlama (mevcut ise): yok.
Bilgilendirilmiş Onam: Katılımcılardan yazılı onam alınmıştır.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.
Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.

Author Contributions: Concept/Design : YT, ET; Data acquisition: ET, YT; Data analysis and interpretation: ET, YT; Drafting manuscript: YT, ET; Critical revision of manuscript: YT; Final approval and accountability: YT, ET; Technical or material support: ET, YT; Supervision: YT; Securing funding (if available): n/a.
Informed Consent: Written consent was obtained from the participants.
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: Authors declared no financial support

REFERENCES

1. Doupis J, Lyons TE, Wu S, Gnardellis C, Dinh T, Veves A. Microvascular reactivity and inflammatory cytokines in painful and painless peripheral diabetic neuropathy. J Clin Endocrinol Metab. 2009;94:2157-63.
2. Fujita T, Hemmi S, Kajiwara M, Yabuki M, Fuke Y, Satomura A et al. Complement-mediated chronic inflammation is associated with diabetic microvascular complication. Diabetes Metab Res Rev. 2013;29:220-6.
3. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes Care. 1999;22:233-40.
4. Wang T, Liu Q, Liu C, Sun L, Li D, Liu A et al. Correlation of echocardiographic epicardial fat thickness with severity of coronary artery disease in patients with acute myocardial infarction. Echocardiography. 2014;31:1177-81.
5. Wu Y, Zhang A, Hamilton DJ, Deng T. Epicardial fat in the maintenance of cardiovascular health. Methodist Debakey Cardiovasc J. 2017;13:20-4.
6. Nunez J, Nunez E, Bodi V, Sanchis J, Minana G, Mainar L et al. Usefulness of the neutrophil to lymphocyte ratio in predicting long-term mortality in ST segment elevation myocardial infarction. Am J Cardiol. 2008;101:747-52.
7. Tamhane UU, Aneja S, Montgomery D, Rogers E-K, Eagle KA, Gurm HS. Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. Am J Cardiol. 2008;102:653-7.
8. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28:1-39.e14.
9. Szuszkiewicz-Garcia MM, Davidson JA. Cardiovascular disease in diabetes mellitus: risk factors and medical therapy. Endocrinol Metab Clin North Am. 2014;43:25-40.
10. Bhat T, Teli S, Rijal J, Bhat H, Raza M, Khoueiry G et al. Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. Expert Rev Cardiovasc Ther. 2013;11:55-9.
11. Tsai JC, Sheu SH, Chiu HC, Chung FM, Chang DM, Chen MP et al. Association of peripheral total and differential leukocyte counts with metabolic syndrome and risk of ischemic cardiovascular diseases in patients with type 2 diabetes mellitus. Diabetes Metab Res Rev. 2007;23:111-8.

12. Azab B, Chainani V, Shah N, McGinn JT. Neutrophil-lymphocyte ratio as a predictor of major adverse cardiac events among diabetic population: a 4-year follow-up study. Angiology. 2013;64:456-65.
13. Valensi P, Avignon A, Sultan A, Chanu B, Nguyen MT, Cosson E. Atherogenic dyslipidemia and risk of silent coronary artery disease in asymptomatic patients with type 2 diabetes: a cross-sectional study. Cardiovasc Diabetol. 2016;15:104.
14. Raffield LM, Hsu FC, Cox AJ, Carr JJ, Freedman BI, Bowden DW. Predictors of all-cause and cardiovascular disease mortality in type 2 diabetes: Diabetes Heart Study. Diabetol Metab Syndr. 2015;7:58.
15. Onat A, Yildirim B, Erer B, Başar Ö, Çetinkaya A, Ceyhan K et al. Total kolesterol/HDL-kolesterol oranı koroner hastalığın en iyi lipid öngördürücüsü: Trigliserid ortalama düzeyimiz yılda 1 mg yükselme gösteriyor. Turk Kardiyol Dern Ars. 2001;29:334-43.
16. Xiao G, Zhu S, Xiao X, Yan L, Yang J, Wu G. Comparison of laboratory tests, ultrasound, or magnetic resonance elastography to detect fibrosis in patients with nonalcoholic fatty liver disease: A meta-analysis. Hepatology. 2017;66:1486-501.
17. Sargeant LA, Bennett FI, Forrester TE, Cooper RS, Wilks RJ. Predicting incident diabetes in Jamaica: the role of anthropometry. Obes Res. 2002;10:792-8.
18. Garcia-Labbe D, Ruka E, Bertrand OF, Voisine P, Costerousse O, Poirier P. Obesity and coronary artery disease: evaluation and treatment. Can J Cardiol. 2015;31:184-94.
19. Lee JJ, Pedley A, Hoffmann U, Massaro JM, Fox CS. Association of changes in abdominal fat quantity and quality with incident cardiovascular disease risk factors. J Am Coll Cardiol. 2016;68:1509-21.
20. Fitzgibbons TP, Czech MP. Epicardial and perivascular adipose tissues and their influence on cardiovascular disease: basic mechanisms and clinical associations. J Am Heart Assoc. 2014;3:e000582.
21. Gonzalez N, Moreno-Villegas Z, Gonzalez-Bris A, Egido J, Lorenzo O. Regulation of visceral and epicardial adipose tissue for preventing cardiovascular injuries associated to obesity and diabetes. Cardiovasc Diabetol. 2017;16:44.
22. Akbas EM, Hamur H, Demirtas L, Bakirci EM, Ozcicek A, Ozcicek F et al. Predictors of epicardial adipose tissue in patients with type 2 diabetes mellitus. Diabetol Metab Syndr. 2014;6:55.
23. Ozcicek A, Ozcicek F, Yildiz G, Timuroglu A, Demirtas L, Buyuklu M et al. Neutrophil-to-lymphocyte ratio as a possible indicator of epicardial adipose tissue in patients undergoing hemodialysis. Arch Med Sci. 2017;13:118-23.